

# RISK ASSESSMENT FOR TORCH COMPLEX INFECTION AGENTS DURING PREGNANCY - PRELIMINARY STUDY

Dan Bogdan Navolan<sup>1\*</sup>, Ioana Mihaela Ciohat<sup>2\*</sup>, Alexandru Erwin Tigla<sup>1</sup>, Dumitrita Vasies<sup>1</sup>, Victor Dumitrascu<sup>3</sup>

## REZUMAT

**Obiectiv:** De a prezenta procentul de gravide din regiunea noastra cu risc de a contacta infectia primara cu agentii infectiosi TORCH in sarcina. **Material si metode:** Au fost testate 660 de gravide in primul trimestru de sarcina pentru detectarea anticorpilor IgG si IgM anti-Toxoplasma Gondii, anti-Citomegalovirus (CMV) si anti-virus rubeolic. Gravidele au fost impartite pe grupe de varsta (in intervale de 1 an). Procentul de gravide imunizate a fost calculat pentru fiecare grup. **Rezultate:** Din cele 660 de gravide testate pentru IgG-anti-Toxoplasma Gondii, 308 au avut un titru pozitiv si 352 un titru negativ, pentru IgG-anti-CMV 618 un titru pozitiv si 42 un titru negativ in timp ce pentru IgG-anti-virus rubeolic, 599 au avut un titru pozitiv si 45 un titru negativ (16 gravide nu au fost testate, datorita faptului ca au fost vaccinate recent). Dintre pacientele testate, 12 gravide au fost pozitive pentru IgM-anti-Toxoplasma Gondii, 6 pozitive pentru IgM-anti-CMV si o gravida pozitiva pentru IgM-anti-virus Rubeolic. Varsta gravidelor s-a incadrat intre 15 si 40 ani; 308 gravide au provenit din mediul urban, 190 din mediul rural iar 162 au schimbat resedinta. **Concluzii:** Aproximativ 54% dintre gravide nu sunt imunizate inainte de sarcina pentru Toxoplasma Gondii, 7% nu sunt imunizate pentru CMV si virusul rubeolic. Aceste gravide sunt susceptibile pentru primoinfectie in sarcina. Datorita riscului de malformatii determinat de primoinfectia cu agentii TORCH in sarcina recomandam efectuarea screeningului fata de acesti agenti indiferent de mediul de provenienta sau de varsta gravidei

**Cuvinte cheie:** agenti TORCH, screening, sarcina, imunizare, distributie pe varste

## ABSTRACT

**Objective:** To present the percentage of gravidas in our area with the risk of contracting primary infections with TORCH-agents during pregnancy. **Material and methods:** There were 660 gravidas tested during the first trimester of pregnancy in order to detect anti-Toxoplasma Gondii, anti-cytomegalovirus (CMV) and anti-rubella IgG/IgM-antibodies. The pregnant women were divided according to age (one-year intervals). The percentage of immunized gravidas was calculated for each group. **Results:** Out of 660 tested gravidas for IgG-anti-Toxoplasma Gondii, 308 were positive and 352 negative, for IgG-anti-CMV 618 were positive and 42 negative and for IgG-anti-rubella, 599 were positive and 45 negative (16 gravidas were not tested, because they have recently been vaccinated). Among the tested patients, 12 were positive for IgM-anti-Toxoplasma Gondii, 6 for IgM-anti-CMV and 1 for IgM-anti-Rubella. The age of the gravidas varies between 15 and 40; 308 live in urban areas, 190 in rural areas and 162 changed their residency. **Conclusions:** About 54% of the gravidas were not immunized before pregnancy for Toxoplasma Gondii, 7% were not immunized for CMV or rubella virus and they could potentially be infected during the first trimester of pregnancy. Due to the fetal malformation risks caused primarily by the infection with TORCH agents during pregnancy, it is strongly recommended to perform TORCH screening tests for all pregnant women, no matter what area they come from (urban/rural) or their age.

**Key Words:** TORCH agents, screening, pregnancy, immunization, age distribution

## INTRODUCTION

The TORCH complex consists of a group of infection agents that can endanger the fetus when the primary infection manifests in a gravida who was not immunized before getting pregnant. The infection agents within this group are: **T**oxoplasma Gondii, other viruses (HIV, varicella, syphilis, etc.), the **R**ubella virus, **C**ytomegaloviruses (CMV) and the **H**erpes simplex virus. The after effects that can manifest in case of infections with these viruses could cause invalidities for the newborn baby. In order to lower the number of cases with fetal complications as a result of infection with these pathogenic agents, it is necessary to implement certain screening methods, biological monitoring during pregnancy, and also informing the patient regarding the necessary hygiene protocols that need to be observed during pregnancy.

<sup>1</sup> Department of Obstetrics and Gynaecology, Victor Babes University of Medicine and Pharmacy Timisoara, <sup>2</sup> Maternal-Fetal Medicine Laboratory, Clinical Emergency Municipal Hospital Timisoara, <sup>3</sup> Department of Laboratory Medicine, Clinical Emergency County Hospital Timisoara

\* The authors contributed equally to this work and should both be regarded as the first author

Correspondence to:

Dan Bogdan Navolan, MD, Department of Obstetrics and Gynaecology - Maternal-Fetal Medicine, 1-3 Odobescu Str., 300202 Timisoara, Tel./ Fax: +40-256491751  
Email: navolan@yahoo.com

Received for publication: Oct. 11, 2008. Revised: Nov. 14, 2008.

*Toxoplasma Gondii* is a common parasitic infection acquired by ingestion of oocytes excreted by cats and contaminating soil or water, or by eating tissue cysts that remain viable in undercooked meat of infected animals.<sup>1,2</sup> Serological surveys demonstrate that world-wide exposure to *Toxoplasma Gondii* is high (30% in US and 50–80% in Europe).<sup>3</sup> In some countries (Austria, France, Belgium) systematic prenatal screening for toxoplasmosis is mandated by law to facilitate early detection of recently acquired infection in pregnant women.<sup>4</sup> Current practice in the United States suggests maternal screening should be done if abnormal fetal findings are detected on ultrasound. These ultrasound findings include hydrocephaly, anatomic abnormalities of the central nervous system, symmetric fetal growth restriction, and non-immune hydrops.<sup>4,5</sup> Maternal testing is considered for all HIV-infected pregnant women and for women with lymphadenopathy, who have negative mononucleosis tests. In the USA Congenital Toxoplasmosis is a neglected infection, particularly in women with inadequate prenatal care.<sup>4</sup>

Cytomegaloviruses are herpes viruses and are recognized as a prevalent cause of congenital infection. Their name derives from the cytopathology they produce. The infected cells become enlarged and contain intra-nuclear and cytoplasmic inclusions. Infection results from exposure to blood products, milk or from intimate contact with infected persons. Most individuals will become infected at some point during their lifetime.<sup>6,7</sup> The seropositive range is between 50% and 80% in Europe and USA and around 90% in Chile, Japan and on the Ivory Coast. The childbearing women acquire CMV at a rate of 2% per year (middle and high socio-economic status) and a rate of 6% per year (lower socio-economic status).<sup>8</sup> Screening for CMV by serology is a debated issue. Routine serologic screening for pregnant women has never been recommended by any public health authority.<sup>9,10</sup> The screening, if done, should be performed at the beginning of pregnancy or even prior to a planned pregnancy. If a woman is seronegative, repeated examinations during pregnancy should be done when there is clinical suspicion. Prenatal testing, however, offers an opportunity to educate women regarding behaviors, and precautionary measures can be suggested to sero-negative women.<sup>11</sup> Moreover, routine antibody testing, especially if done before pregnancy, may help to differentiate between primary and secondary infection in cases of suspected CMV infection during pregnancy.<sup>12</sup> Naessens et al. evaluated a screening program for CMV in which serological testing was performed at the first prenatal visit; they showed that such screening

allows the detection of 82% of all congenital CMV infections.<sup>13</sup> Nevertheless, routine serologic testing of all pregnant women for CMV to identify those who have acquired primary infection during pregnancy is not currently recommended. Therefore, serological testing for CMV should be used only in women who develop influenza-like symptoms during pregnancy or following detection of sonographic findings that are suggestive of CMV infection and cannot be explained by another cause (placental insufficiency in case of IUGR and oligohydramnios and fetal anemia in case of ascites etc.). According to Canadian Society of Obstetricians and Gynecologists routine screening of pregnant women for CMV by serology testing is currently not recommended. Level III-B.<sup>9</sup>

The Rubella virus infection is the first virus demonstrated as teratogen.<sup>14</sup> Rubella is a contagious disease transmitted via the respiratory system with an incubation time of 2 weeks. Viremia occurs 5 to 7 days after contact and the transplacental infection is possible during this phase.<sup>15</sup> The specific clinical features represent a characteristic rash starting on the face and gradually passing down through the body to the feet, generally preceded by fever, lymphadenopathy and arthralgia, and also respiratory symptoms.<sup>16</sup> During pregnancy the Rubella virus infection can cause severe illness of the fetus and the newborn. There is a high risk in fetuses of gravidas without immunological protection to develop congenital Rubella syndrome (CRS) if the infection occurs in the first trimester of pregnancy.

Screening is usually done before pregnancy for diseases such as rubella and varicella against which immunization can be provided.

## **MATERIALS AND METHODS**

The data was analyzed retrospectively from 660 gravidas that were tested in the first trimester of pregnancy for the presence of IgG/IgM anti-*Toxoplasma Gondii*, IgG/IgM anti-cytomegalovirus (CMV) and IgG/IgM anti-rubella antibodies. The sera were investigated by the chemiluminescence method, using an Immulite One Machine (DPC, Diagnostic Products Corporation, Los Angeles, USA). The IgG anti-*Toxoplasma Gondii* and IgG anti-rubella were determined quantitatively while IgM anti-*Toxoplasma Gondii*, IgG/IgM anti-cytomegalovirus and IgM anti-rubella were determined qualitatively. A cut-off (CO) was calculated for each type of qualitative assay. The calculations of the results determiners were done according to the following formula: sample cps/CO. The data of pregnancy and the acquired data storage

has been performed through the ASTRAIA software, the maternal-fetal module (Astraiia GmbH, Munich, Germany, www.astraiia.de). The results were correlated with the gestational age of the gravida. The data was analyzed with EPI INFO™ 7 Software. The graphics were generated in Microsoft Excel.

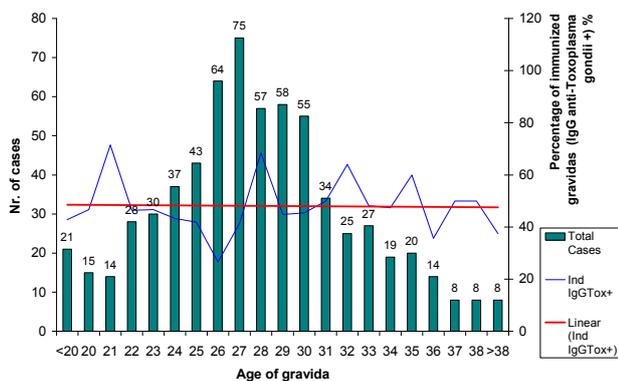
## RESULTS

### 1. Characteristics of the gravida group (age, residency)

660 gravidas who came directly through ward physicians of the Municipal Obstetrics and Gynecology Hospital in Timisoara, were evaluated during the first trimester of pregnancy for the immune status for the TORCH complex agents. The age of the gravidas varied between 15 and 40 years old. 308 (46.67%) live in urban areas and 190 (28.78%) in rural areas, and 162 (24.54%) have changed their residency. Due to the low number of gravidas for each age group, the patients with ages under 20 and over 38 were also included in this group.

### 2. Percentage of immunized gravidas to Toxoplasma Gondii within the studied group

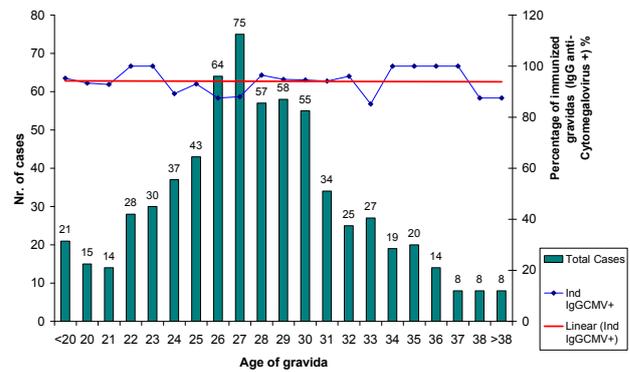
Out of 660 gravidas tested for IgG-anti-Toxoplasma Gondii antibodies, 308 had positive titer values and 352 had negative values. 12 gravidas were positive for IgM-anti-Toxoplasma Gondii antibodies. The percentage of immunized gravidas for Toxoplasma Gondii during the first trimester of pregnancy was around 46% with small variations according to the age of the gravidas. (Fig. 1)



**Figure 1.** Distribution of number of gravidas (ordinata 1), percentage of immunized gravidas to Toxoplasma Gondii and trend line (ordinata 2) on gravidas grouped according to age (abscissa).

### 3. Percentage of immunized gravidas to cytomegalovirus within the studied group

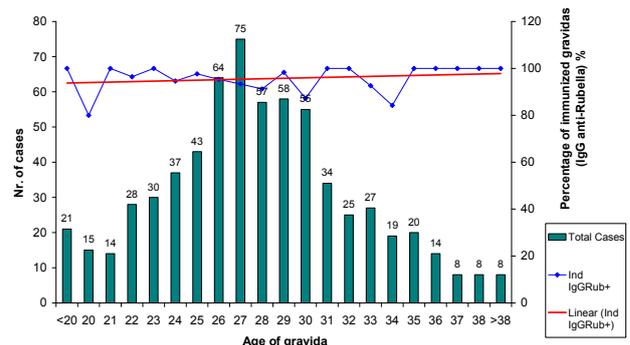
Out of the 660 gravidas tested for IgG-anti-CMV antibodies, 618 pregnant women were positive and 42 were negative, and 6 were positive for IgM-anti-CMV antibodies. The average percentage of immunized gravidas is about 93%. (Fig. 2)



**Figure 2.** Distribution of number of gravidas (ordinata 1), percentage of immunized gravidas to cytomegalovirus and trend line (ordinata 2) on gravidas grouped according to age (abscissa).

### 4. Percentage of immunized gravidas to Rubella virus within the studied group

Out of the 660 gravidas in the study for IgG-anti-rubella antibodies, 599 were positive and 45 were negative, while 16 gravidas were not tested and considered with IgG-anti-rubella antibodies positive because of the anamneses vaccination mentioned.. One gravida was positive for IgM-anti-rubella antibodies. The average percentage of immunized gravidas is about 93%. (Fig. 3)



**Figure 3.** Distribution of number of gravidas (ordinata 1), percentage of immunized gravidas to Rubella virus and trend line (ordinata 2) on gravidas grouped according to age (abscissa).

## DISCUSSIONS

The pathogenic agents included in the TORCH complex could cause damage to the embryo, the fetus and to the newborn, in case of a primary infection manifested during the pregnancy.<sup>2,8,16</sup> The consequences upon the fetus will be invalidities unless a prompt treatment is administered. Some studies show that fetus infection may manifest in case of an infection in an immunized pregnant woman when she has been immunized for that particular agent (Toxoplasma Gondii, Cytomegalovirus) before pregnancy, although it is much lower in intensity.<sup>6,15</sup>

In the situation of an acute infection, there is the possibility of implementing some therapeutic

measures that will greatly reduce the rate of fetal complications.<sup>17-21</sup>

Implementing a systematic screening requires a public or private effort, which needs to be supported by a cost-efficiency analysis.<sup>1,3,6,21,22</sup> In this regard, the results of this study are very useful because they present the percentage of susceptible gravidas to contact a primary infection, according to age groups: 54% with *Toxoplasma Gondii* and 9% with cytomegalovirus. Indirectly, the attention is brought upon the necessity of including counseling during pregnancy, regarding the hygiene measures that need to be taken in order to prevent the following infections: *Toxoplasma Gondii*, Cytomegalovirus and Rubella virus.

Also, certain immunological investigations are recommended in order to explore the status of immunization for the pregnant women that have unspecific manifestations, similar to those determined by one of the TORCH agents.

All the agents described above have the potential to damage the fetus if an infection occurs in a non-immune-competent gravida. In conclusion, all efforts must be done to recognize these gravidas and to counsel this group of patients. If an infection occurs the gravida must be adequately counseled and treated, if possible.

In case of a primary *Toxoplasma Gondii* infection in pregnancy the therapy recommendations vary in different countries: in France spiramycin is prescribed immediately after diagnosis of maternal infection and changed to a pyrimethamine-sulphonamide combination if fetal infection is diagnosed or if it is acquired in late pregnancy and in Austria gravidas initially receive pyrimethamine-sulphonamide (after 15 weeks of gestation), and change to spiramycin if fetal diagnosis is negative.<sup>3,19,20</sup>

If the diagnosis of congenital CMV infection is confirmed, one option is pregnancy termination. A second proposed option has been to treat the mother with antiviral agents such as ganciclovir, foscarnet, and cidofovir. These drugs are of moderate effectiveness in treating CMV infection in the adult, particularly in the immune-compromised patient. However, they are not of proven value in preventing or treating congenital CMV infection. The most promising therapy for congenital CMV infection appears to be hyper immunoglobulin. Nigro et al described the use of hyper immunoglobulin for the treatment of a mother who had a twin pregnancy, as being discordant for congenital CMV infection. Treatment was administered at 22 weeks' gestation. The patient received hyper immunoglobulin, 200 units/kg/day intravenously for three days. A separate dose of 400

units of hyper immunoglobulin was injected intra-amniotically into the sac of the affected twin. The authors noted that treatment resulted in decreased placental edema, improvement in fetal growth, an increase in IgG avidity, and an increase in maternal cell-mediated immunity. At nine months of age, both infants were negative for CMV.<sup>23</sup>

The results of the article could be useful for the obstetrics physicians and for generalists in order to appreciate the degree of immunization of pregnant women for *Toxoplasma Gondii*, cytomegalovirus and the rubella virus and also for evaluating the necessity of recommending these investigations for the gravidas. The study brings information regarding the degree of susceptibility of gravidas to TORCH agents, providing the finances of the health system, in order to make cost-efficient calculations for evaluating the necessity of including these investigation packages of medical assistance during pregnancy. This aspect could be tremendously important in the context of new health laws, where there will be competitive insurance policies offered for investigations for both the insurant and the clinics. The adequate assessment and implementation of a screening program could reduce costs in the system and could also increase the safety of the medical act. Also, repeating these investigations during pregnancy for some selected gravidas could contribute to the detection of cases that require treatment.

## CONCLUSIONS

The immunization measures through vaccination with anti-Rubella virus decreased the percentage of gravidas susceptible to primary infection with Rubella virus during pregnancy. Due to the high percentage of unimmunized gravidas to TORCH agents, it is best to screen all the pregnant women, no matter their residency (urban or rural) or age, because about 54% of gravidas are not immunized for *Toxoplasma Gondii* and 7% for CMV and rubella virus, so they are potentially in danger of infection during the first trimester of pregnancy. This is very useful information for public and private insurance houses, the institutions that will sign their contracts with the patients and the hospitals according to the new health laws. An adequate cost efficient assessment could reduce the high costs determined by the manifestations of these infections during pregnancy.

The non-immunized gravidas need to be reassessed during their pregnancy, and the ones with unspecific symptomatology, possibly TORCH, need to be immunologically reinvestigated. For the patients with infections caused by TORCH agents during

pregnancy, there are therapeutic measures that can be implemented.

## **ACKNOWLEDGEMENTS**

Supported in part by the National Authority of Scientific Research (Bucharest, Romania) - Grant POS CCE-A2-0.2.2.4-2008-2 No. 36/11.05.2009, and Grant POS CCE-A2-0.2.2.4-2009-3 No. 202/15.07.2010.

## **REFERENCES**

1. Cook AJ, Gilbert RE, Buffalano W, et al. for the European Research Network on Congenital Toxoplasmosis. Sources of toxoplasma infection in pregnant women: European multicentre case-control study. *BMJ* 2000; 321: 142-47.
2. Remington J, McLeod R, Thulliez P, et al. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*. Philadelphia: WB Saunders, 2001, p. 205-346.
3. Rorman E, Zamir CS, Rilkis I, et al. Congenital toxoplasmosis – prenatal aspects of *Toxoplasma Gondii* infection. *Reprod Toxicol* 2006;21:458-472.
4. Stillwaggon E, Carrier CS, Sautter M, et al. Maternal serologic screening to prevent congenital toxoplasmosis: a decision-analytic economic model. *PLoS Negl Trop Dis*. 2011 Sep;5(9):e1333. Epub 2011 Sep 27.
5. Pinard JA, Leslie NS, Irvine PJ. Maternal serologic screening for toxoplasmosis. *J Midwifery Womens Health*. 2003 Sep-Oct;48(5):308-16.
6. Guerina N. Cap. 21. Management of Cytomegalovirus and *Toxoplasma Gondii* in pregnancy. In: S.D. Craigo, E.R. Baker. eds. *Medical complication in pregnancy: Practical pathways in obstetrics and gynecology*. McGraw-Hill Medical Publishing Division, 2005:359-381.
7. Goldberg JM, Ziel HK, Burchette R. Evaluation of CMV, varicella immune status in an obstetrical population in relation to place of birth. *Am J Perinatol* 2002;19:387-394.
8. Stagno S. Cytomegalovirus. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*, 4th ed. Philadelphia Saunders, 2001, p. 389-424.
9. Cytomegalovirus infection in pregnancy - SOGC Clinical Practice Guide – No. 240, April 2010.
10. Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. *Clin Microbiol Rev* 2002;15:680-715.
11. Demmler GJ. Screening for congenital cytomegalovirus infection: a tapestry of controversies, *J Pediatr* 2005;146:162-4.
12. Ornoy A, Diav-Citrin O. Fetal effects of primary and secondary cytomegalovirus infection in pregnancy. *Reprod Toxicol* 2006;21:399-409.
13. Naessens A, Casteels A, Decatte L, et al. A serologic strategy for detecting neonates at risk for congenital cytomegalovirus infection. *J Pediatr* 2005;146:194-7.
14. De Santis M, Cavaliere AF, Straface G, et al. Rubella infection in pregnancy. *Reprod Toxicol*. 2006 May;21(4):390-8.
15. *Epidemiology and prevention of vaccine preventable disease. The Pink Book*, 8th Ed. February 2004. available in <http://www.cdc.gov/nip/publication/pink>.
16. Pandolfi E, Chiaradia G, Moncada M, et al. Prevention of congenital rubella and congenital varicella in Europe. *Euro Surveill*. 2009 Mar 5;14(9):16-20.
17. Valdès V, Legagneur H, Watrin V, et al. Congenital toxoplasmosis due to maternal reinfection during pregnancy, *Arch Pediatr*. 2011 Jul;18(7):761-3. Epub 2011 May 19. French.
18. Duff P. *Diagnosis and Management of CMV Infection in Pregnancy*, *Perinatology* 2010; 1:1-6.
19. Thiébaud R, Leproust S, Chêne G, et al. Effectiveness of prenatal treatment for congenital toxoplasmosis a meta-analysis individual patients data. *Lancet*. 2007 Jan 13;369(9556):115-22.
20. European Multicentre Study on Congenital Toxoplasmosis. Effect of timing and type of treatment on the risk of mother to child transmission of *Toxoplasma Gondii*. *BJOG* 2003; 110: 112-20.
21. Yinon Y, Farine D, Yudin MH. Screening, diagnosis, and management of cytomegalovirus infection in pregnancy. *Obstet Gynecol Surv*. 2010 Nov;65(11):736-43.
22. WHO position paper. Rubella vaccines: *Wkly Epidemiol Rec*. 2011 Jul 15;86(29):301-16.
23. Nigro G, LaTorre, Anceschi MM, et al. Hyperimmunoglobulin therapy for a twin fetus with cytomegalovirus infection and growth restriction. *Am J Obstet Gynecol* 1999;180:1222-6.